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78464 Konstanz (DE). KLEY, Hans-Peter; Im Weinberg
3b, 78476 Allensbach (DE).

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(72) Inventor; and

(75) Inventor/Applicant (*for US only*): STERK, Jan, Geert
[NL/NL]; Stadhouderslaan 38, NL-3583 JJ Utrecht (NL).

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(74) Common Representative: BYK GULDEN LOMBERG
CHEMISCHE FABRIK GMBH; Patentabteilung, Byk-
Gulden-Strasse 2, 78467 Konstanz (DE).

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(54) Title: PHTHALAZINONE DERIVATIVES AS PD3/4 INHIBITORS

(57) Abstract: The compounds of formula (I), in which R1, R2, R3, R4, R5, R6, X and Y have the meanings as given in the description are novel effective bronchial therapeutics.

PHTHALAZINONE DERIVATIVES AS PD3/4 INHIBITORS

Field of application of the invention

The invention relates to novel Phthalazinones, which are used in the pharmaceutical industry for the production of medicaments.

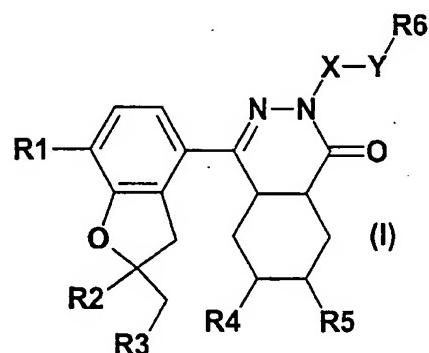
Known technical background

International Patent Applications WO98/31674, WO99/31071 and WO99/31090 disclose phthalazinone derivatives having selective PDE4 inhibitory properties. In the International Patent Application WO94/12461 and in the European Patent Application EP 0 763 534 3-aryl-pyridazin-6-one respectively arylalkyl-diazinone derivatives are described as selective PDE4 inhibitors.

Description of the invention

It has now been found that the phthalazinones, which are described in greater details below, have surprising and particularly advantageous properties.

The invention thus relates to compounds of the formula I



in which

- R1 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
- R2 is 1-4C-alkyl and
- R3 is hydrogen or 1-4C-alkyl,
or wherein

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R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R4 and R5 are both hydrogen or together form an additional bond,

and in which either

X is a covalent bond and

Y is a covalent bond,

or

X is $-C_nH_{2n}-$ and

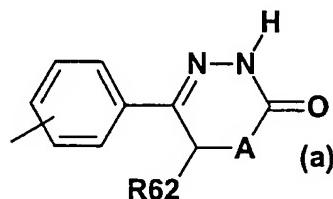
Y is O (oxygen), S (sulfur), carboxylate ($-C(O)-O-$), carboxamido ($-C(O)NH-$) or sulfonamido ($-S(O)_2NH-$),

or

X is phenylene and

Y is carboxylate ($-C(O)O-$), carboxamido ($-C(O)NH-$) or sulfonamido ($-S(O)_2NH-$),

R6 represents a radical of formula (a)



wherein

A is S (sulphur) or $-CH(R61)-$,

R61 is hydrogen or 1-4C-alkyl,

R62 is hydrogen or 1-4C-alkyl, or wherein

R61 and R62 together form an additional bond,

n is an integer from 1 to 6,

and the salts of these compounds.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

3-5C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy and cyclopentyloxy.

3-5C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy group are replaced by fluorine atoms.

As spiro-linked 5-, 6- or 7-membered hydrocarbon rings, optionally interrupted by an oxygen or sulphur atom, may be mentioned the cyclopentane, cyclohexane, cycloheptane, tetrahydrofuran, tetrahydropyran and the tetrahydrothiophen ring.

Possible radicals $-C_nH_{2n}-$ are straight chain or branched radicals. Examples which may be mentioned are the hexylene, pentylene, butylene, isobutylene, sec-butylene, tert-butylene, propylene, isopropylene, ethylene and the methylene radical.

Suitable salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

Compounds of the formula I to be emphasized are those in which

R1 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is 1-4C-alkyl and

R3 is hydrogen or 1-4C-alkyl,

or wherein

R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

R4 and R5 are both hydrogen or together form an additional bond,

and in which either

X is a covalent bond and

Y is a covalent bond

or

X is $-C_nH_{2n}-$ and

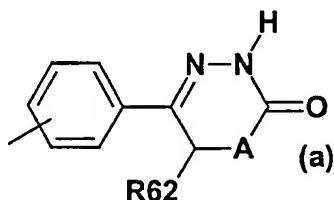
Y is O (oxygen), carboxamido ($-C(O)NH-$) or sulfonamido ($-S(O)_2NH-$),

or

X is phenylene and

Y is carboxamido ($-C(O)NH-$) or sulfonamido ($-S(O)_2NH-$),

R6 represents a radical of the formula (a)



wherein

A is S (sulphur) or $-CH(R61)-$,

R61 is hydrogen or 1-2C-alkyl,

R62 is hydrogen or 1-2C-alkyl, or wherein

R61 and R62 together form an additional bond,

n is an integer from 1 to 6,

and the salts of these compounds.

Compounds of the formula I which are particularly to be emphasized are those in which

R1 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is 1-4C-alkyl and

R3 is hydrogen or 1-4C-alkyl,

or wherein

R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane or cyclohexane ring,

R4 and R5 are both hydrogen or together form an additional bond,

and in which either

X is a covalent bond and

Y is a covalent bond

or

X is $-C_nH_{2n}-$ and

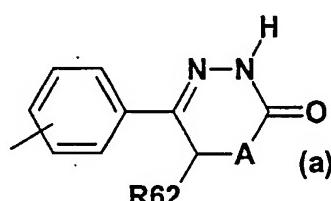
Y is O (oxygen) or carboxamido (-C(O)NH-)

or

X is phenylene and

Y is carboxamido (-C(O)NH-),

R6 represents a radical of formula (a)



wherein

A is S (sulphur) or $-CH(R61)-$,

R61 is hydrogen,

R62 is methyl, or wherein

R61 and R62 together form an additional bond,

n is an integer from 1 to 6,

and the salts of these compounds.

Preferred compounds of formula I are those in which

R1 is methoxy or difluoromethoxy,

R2 is methyl,

R3 is hydrogen,

or wherein

R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane ring,

or wherein

R4 and R5 together form an additional bond,

and in which either

X is a covalent bond and

Y is a covalent bond

or

X is $-C_nH_{2n}-$ and

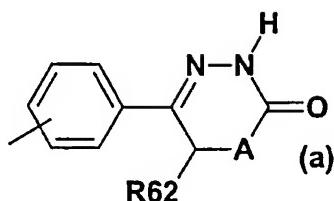
Y is O (oxygen) or carboxamido ($-C(O)NH-$)

or

X is phenylene and

Y is carboxamido ($-C(O)NH-$),

R6 represents a radical of formula (a)



wherein

A is S (sulphur) or $-CH(R61)-$,

R61 is hydrogen,

R62 is methyl, or wherein

R61 and R62 together form an additional bond,

n is an integer from 1 to 6,

and the salts of these compounds.

Especially preferred compounds of formula I are those in which

R1 is methoxy,

R2 is methyl,

R3 is hydrogen,

or wherein

R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane ring,

R4 and R5 together form an additional bond,

and in which either

X is a covalent bond and

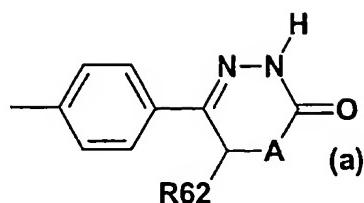
Y is a covalent bond

or

X is $-(CH_2)_6-$ and

Y is O (oxygen),

R6 represents a radical of formula (a)



wherein

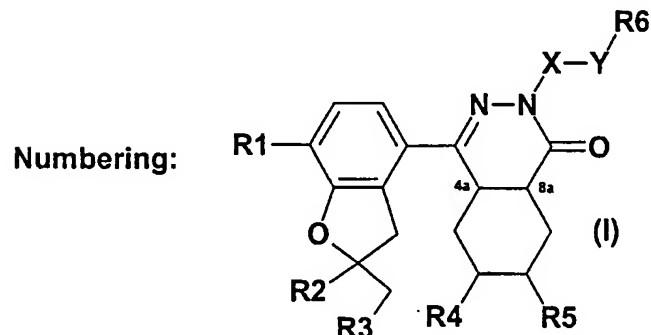
A -CH(R61)-,

R61 is hydrogen,

R62 is methyl,

and the salts of these compounds.

The compounds of formula I are chiral compounds with a chiral center in the dihydrofuran-ring, if the substituents -R2 and -CH₂R3 are not identical. However, preferred are those compounds, in which the substituents -R2 and -CH₂R3 are identical or together and with inclusion of the carbon atoms to which they are bonded form a spiro-connected 5-, 6- or 7-membered hydrocarbon ring. Additional chiral centers exist in the positions 4a and 8a

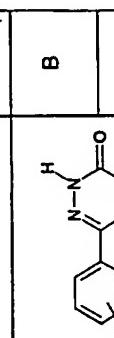
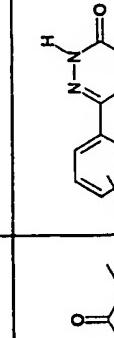
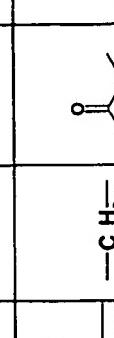
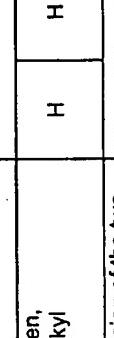
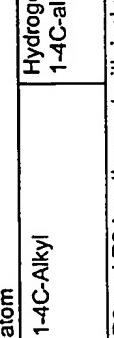
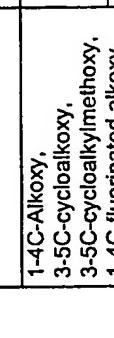


Therefore the invention includes all conceivable pure diastereomers and pure enantiomers, as well as all mixtures thereof independent from the ratio, including the racemates. Preferred are those compounds, in which the hydrogen atoms in the positions 4a and 8a are cis-configurated. Especially preferred in this connection are those compounds, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a. Racemates can be split up into the corresponding enantiomers by methods known by a person skilled in the art. Preferably the racemic mixtures are separated into two diastereomers with the help of an optical active separation agent on the stage of the cyclohexanecarboxylic acids or the 1,2,3,6-tetrahydrobenzoic acids (for example, starting compound A3). As separation agents may be mentioned, for example, optical active

amines such as the (+)- and (-)-forms of α -methylbenzylamine and ephedrine, or the optical active alkaloids quinine, cinchonine, cinchonidine and brucine.

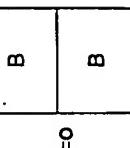
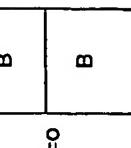
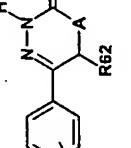
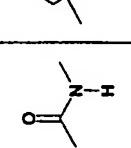
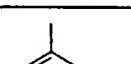
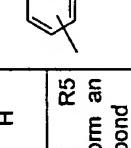
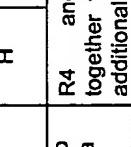
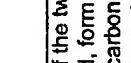
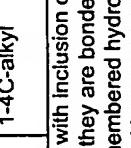
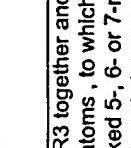
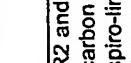
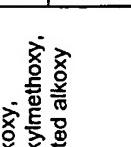
The invention further relates to processes for the preparation of compounds of formula I and their salts (compare Table 1).

Table 1: Preparation Methods

R1	R2	R3	R4	R5	X	Y	R6	Method
1-4C-Alkoxy, 3-5C-cycloalkyloxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H	covalent bond	covalent bond		A
1-4C-Alkoxy, 3-5C-cycloalkyloxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H	R4 and together form an additional bond	covalent bond		A
1-4C-Alkoxy, 3-5C-cycloalkyloxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H	R4 and together form an additional bond	—C _n H _{2n} —		B
1-4C-Alkoxy, 3-5C-cycloalkyloxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H	R4 and together form an additional bond	—C _n H _{2n} —		B
1-4C-Alkoxy, 3-5C-cycloalkyloxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H	R4 and together form an additional bond	—C _n H _{2n} —		B
1-4C-Alkoxy, 3-5C-cycloalkyloxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H	R4 and together form an additional bond	—C _n H _{2n} —		B

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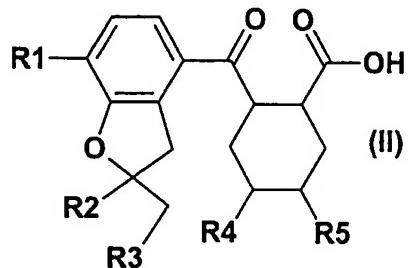
Continuation of Table 1

R1	R2	R3	R4	R5	X	Y	R6	Method
1-4C-Alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H		O, S		C
			R4 and R5 together form an additional bond					C
1-4C-Alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H				B
			R4 and R5 together form an additional bond					B
1-4C-Alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H				B
			R4 and R5 together form an additional bond					B
1-4C-Alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, 1-4C-fluorinated alkoxy	1-4C-Alkyl	Hydrogen, 1-4C-alkyl	H	H				B
			R4 and R5 together form an additional bond					B

II

Method A:

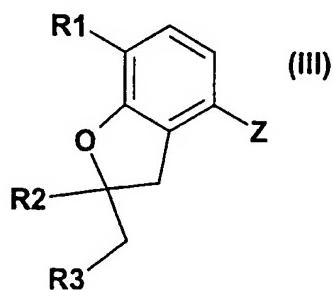
Compounds of formula I in which R1, R2, R3, R4, R5 and R6 have the above-mentioned meanings and X and Y represent a covalent bond are preferably prepared by reacting a keto acid of formula II



or one of its reactive derivatives, in which R1, R2, R3, R4 and R5 have the above-mentioned meanings with a hydrazine derivative of the formula R6-NH-NH₂ in which R6 has the above-mentioned meanings.

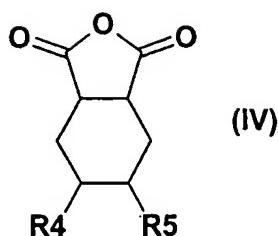
The reaction of the keto acids of formula II or one of their reactive derivatives with a hydrazine derivative of formula R6-NH-NH₂ is advantageously carried out with one to three equivalents of the hydrazine derivatives of formula R6-NH-NH₂. As solvent are preferably used alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isoamylalcohol, ethers, glycols and their ethers such as ethylene glycol, diethylene glycol, ethylene glycol monomethyl or ethylene glycol monoethyl ether and especially water soluble ethers such as tetrahydrofuran or dioxane; further toluene or benzene, especially when the method of azeotropic distillation is used to remove the reaction water.

Keto acids of the formula II, in which R1, R2, R3, R4 and R5 have the above-mentioned meanings can, for example, be prepared from compounds of the formula III,



in which R1, R2 and R3 have the above-mentioned meanings and Z represents hydrogen (H) by Friedel-Crafts acylation with compounds of the formula IV,

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in which R4 and R5 have the above-mentioned meanings. The Friedel-Crafts acylation is carried out in a manner which is known by the skilled person (for example as described in M. Yamaguchi et al., J. Med. Chem. 36: 4052-4060, 1993) in presence of a suitable catalyst, such as for example, AlCl_3 , ZnCl_2 , FeCl_3 or iodine, in an appropriate inert solvent, such as methylene chloride or nitrobenzene or another inert solvent such as diethylether, preferably at raised temperature, in particular at the boiling point of the solvent used.

Alternatively, the compounds of formula II, in which R1, R2, R3, R4 and R5 have the above-mentioned meanings, can be prepared from compounds of the formula III, in which R1, R2 and R3 have the above-mentioned meanings and Z represents a halogen atom through reaction with compounds of the formula IV, in which R4 and R5 have the above-mentioned meanings.

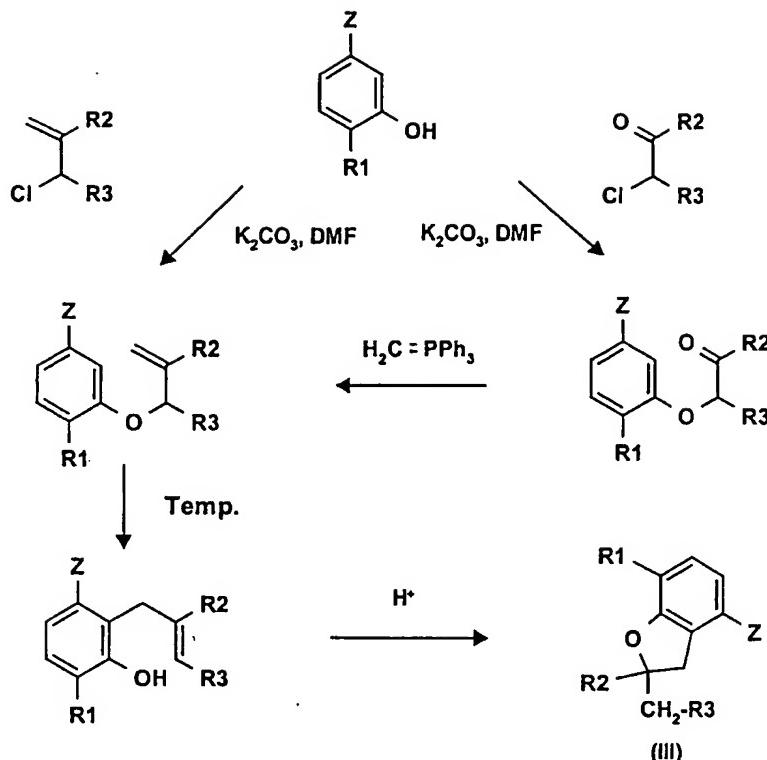
The alternative reaction, which is mentioned in the previous paragraph is carried out in a manner which is known by a person skilled in the art, for example

- a) by activating compounds of formula III, in which R1, R2, R3 and Z have the above-mentioned meanings, by a lithium/halogen exchange reaction at low temperatures (preferably at -60 to -100°C) in an appropriate inert solvent such as tetrahydrofuran or diethylether, preferably under an atmosphere of inert gas, followed by reaction of the lithiated compounds with cyclic carboxylic acid anhydrides of formula IV, or
- b) by converting compounds of formula III in which R1, R2, R3 and Z have the above-mentioned meanings, in a suitable inert solvent such as, for example, tetrahydrofuran or diethylether into the corresponding Grignard compounds of formula III in which Z represents MgCl , MgBr or MgI followed by reaction of the Grignard compounds with cyclic carboxylic acid anhydrides of formula IV, in which R4 and R5 have the above-mentioned meanings.

Compounds of formula III, in which R1, R2 and R3 have the above-mentioned meanings and Z represents a hydrogen (H) or halogen atom, are known or can be prepared according to reaction scheme 1.

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Scheme 1



By way of example, the preparation of compounds of the formula III is described in the following examples under "starting compounds". The preparation of further compounds of formula III can be carried out in an analogous manner.

Compounds of formula IV, in which R4 and R5 have the above-mentioned meanings are as well known or can be prepared by methods known by a person skilled in the art.

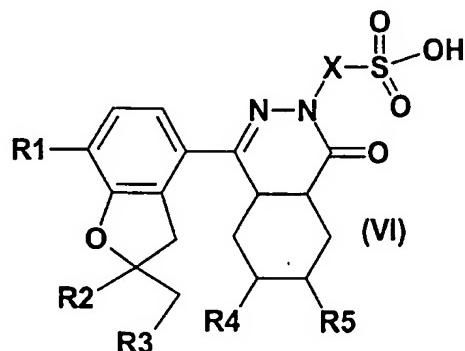
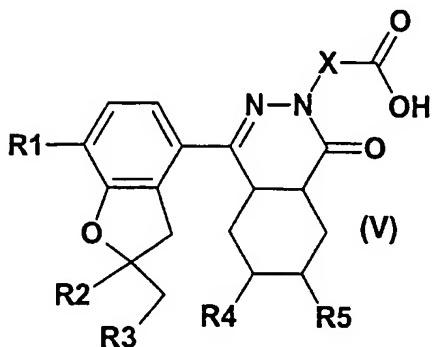
The preparation of hydrazine derivatives of formula R₆-NH-NH₂ is described, for example, by A. Mertens et al. in J.Med.Chem. 33, 2870-2875, 1990. Further hydrazine derivatives of formula R₆-NH-NH₂, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods.

Method B:

Compounds of formula I in which R1, R2, R3, R4, R5 and R6 have the above-mentioned meanings, X represents $-C_nH_{2n-}$ or phenylene and Y represents a carboxylate group ($-C(O)O-$), a carboxamido group ($-C(O)NH-$) or a sulfonamido group ($-SO_2-NH-$) are preferably prepared by reacting an acid of formula V or an sulfonic acid of formula VI or one of their reactive derivatives (for example an acid halide, an ester

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or a sulfonyl halide) in which R1, R2, R3, R4 and R5 have the above-mentioned meanings and X represents $-C_nH_{2n}-$ or phenylene with a phenol of formula R6-OH or an amine of formula R6-NH₂, in which R6 has the above-mentioned meanings.



The reactions can be performed using customary reaction conditions for example as described in the following examples.

The carboxamide linkage can also be prepared using any coupling method described by M. Bodansky and A. Bodansky in "The Practice of Peptide Synthesis", Springer Verlag, Berlin 1984.

Standard procedures for the preparation of sulfonamides starting from sulfonylchlorides and amines are known to the person skilled in the art.

Acids of formula V or sulfonic acids of formula VI in which X represents phenylene can be prepared analogously to the method described under method A starting from compounds of formula II using a hydrazine derivative such as for example hydrazinobenzoic acid or hydrazinobenzenesulfonic acid.

Acids of formula V or sulfonic acids of formula VI in which X represents $-C_nH_{2n}-$ can in a first step also be prepared analogously to the method described under method A starting from compounds of formula II using hydrazine hydrate instead of a hydrazine derivative of formula R6-NH-NH₂. Deprotonation of the N-H group followed by an alkylation step yields the acids of formula V or the sulfonic acids of formula VI.

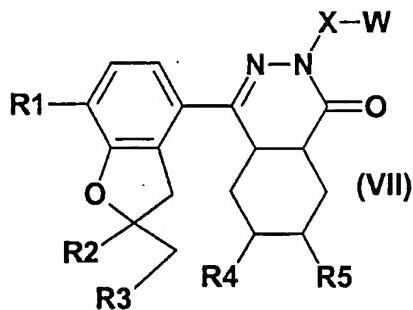
The hydrogen atom of the NH-group is removed by a base such as, for example, potassium carbonate, sodium hydroxide, sodium hydride, sodium methanolat or sodium ethanolate in a suitable inert solvent such as dimethylformamide, dimethylsulfoxide, tetrahydrofuran or diethylether. As appropriate alkylation reagents may be mentioned, for example, 4-bromobutanoic acid, ethyl bromacetate or 4-bromobutanesulfonic acid.

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Amines of formula R₆-NH₂ can be prepared, for example, as described by Edgar A. Steck et al., J. Heterocyclic Chem. 1974, 11, 755-761 or as described by B.E. Burpitt in J. Heterocyclic Chemistry, 25, 1689-1695, 1988. Phenols of formula R₅-OH can be prepared, for example, as described in EP 0 178 189.

Method C:

Compounds of formula I in which R₁, R₂, R₃, R₄, R₅ and R₆ have the above-mentioned meanings, X represents -C_nH_{2n}- and Y represents an oxygen or a sulphur atom are preferably prepared by reacting a compound of formula VII



in which R₁, R₂, R₃, R₄ and R₅ have the above-mentioned meanings, X represents -C_nH_{2n}- and W represents a suitable leaving group, for example a halogen atom, preferably bromine, with a phenol of formula R₆-OH or a thiophenol of formula R₆-SH, in which R₆ has the above-mentioned meanings.

The reaction is preferably carried out under basic conditions in an inert solvent like dimethylformamide, dimethylsulfoxide or tetrahydrofuran.

The compounds of formula VII can be prepared analogously to the method described for the corresponding acids of formula V under method B using in the alkylation step ω,ω' -dihalogenalkanes instead of the ω,ω' -halogenalkanoic acids.

The preparation of phenols of formula R₆-OH is described under Method B. Further phenols or thiophenoles of formula R₆-OH (R₆-SH) can be prepared in an analogous way.

Suitably, the conversions are carried out analogous to methods which are familiar per se to the person skilled in the art, for example, in the manner which is described in the following examples.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the residue obtained from a suitable solvent or

subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

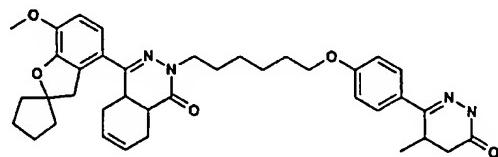
Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification or by acidifying into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds of formula I, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods.

The compounds, which are mentioned in the examples as well as their salts are preferred compounds of the invention.

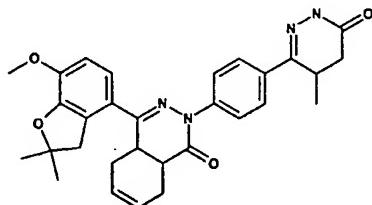
ExamplesFinal products

1. (cis)-4-(2,3-dihydro-7-methoxybenzofuran-2-spiro-1'-cyclopentan-4-yl)-2-[6-[4-(4,5-dihydro-5-methyl-3-oxo-2H-pyridazin-6-yl)-phenoxy]hexyl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one



A mixture of 1.0 g of starting compound A1, 0.5 g of starting compound A7 and 1.0 g of potassium carbonate in 10 ml of DMF is stirred for 40 h at RT. After the addition of 50 ml of water, the mixture is extracted with diethyl ether (3x100 ml). The ether layer is dried over magnesium sulfate and evaporated. The residue is purified by chromatography [silica; ethyl acetate:petroleum ether (60-80°C)/1:1]. The title compound is crystallised from diethyl ether. M. p. 166-169°C.

2. (cis)-4-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-yl)-2-[4-(4,5-dihydro-5-methyl-3-oxo-2H-pyridazin-6-yl)-phenyl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one



A mixture of 5 mmol of starting compound A8 and 8 mmol of starting compound A10 in 20 ml of pyridine is refluxed for 24 hours. After evaporating the solvent, the residue is dissolved in about 150 ml of ethyl acetate and this solution is washed successively with 1 N HCl (2x) and with aqueous sodium carbonate. After drying over magnesium sulfate, the solvent is evaporated and the residue purified by column chromatography using a mixture of ethyl acetate and petroleum ether [60-80°C] (1/1) as eluents. The title compound is crystallized from diethyl ether. M. p. 220-221°C

Starting Compounds**A1. (cis)-2-(6-bromo-1-hexyl)-4-(2,3-dihydro-7-methoxybenzofuran-2-spiro-1'-cyclopentan-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one**

A mixture of 5 g of A2, 20 g of 1,6-dibromohexane and 10 g of potassium carbonate in 50 ml of DMF is stirred at RT for 18 h. After the addition of 200 ml of water, the mixture is extracted with diethyl ether (3 x 200ml). The ether layer is dried over magnesium sulfate and evaporated. The residue is crystallised from petroleum ether (60-80°C). M. p. 80-82°C

A2. (cis)-4-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1'-cyclopentan-4-yl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one

A solution of 8 g of A3 and 10 g of hydrazine hydrate in 100 ml of ethanol is refluxed for 3 hours. After evaporating the solvent, the residue is partitioned between ethyl acetate and aqueous sodium carbonate. The organic layer is dried over magnesium sulfate and concentrated under reduced pressure upon which the compound crystallises. M. p. 193-194°C

A3. (cis)-2-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1'-cyclopentane-4-carbonyl)-1,2,3,6-tetrahydrobenzoic acid

A solution of 35 g of compound A4 in 350 ml tetrahydrofuran is added slowly to 3.5 g of magnesium in 50 ml of tetrahydrofuran. After complete addition, the mixture is refluxed for 5 h and left at room temperature for additional 18 h. This mixture is added slowly to a solution of 18.8 g of (cis)-1,2,3,6-tetrahydrophthalic anhydride in tetrahydrofuran at 0°C. After complete addition the mixture is refluxed for 6 h and left at room temperature for additional 18 hours after which the reaction is quenched with ammonium chloride and the solvent removed under reduced pressure. The residue is acidified with concentrated hydrochloric acid and the mixture extracted with ethyl acetate. The organic layer is dried over magnesium sulfate and evaporated. The residue is purified by chromatography (petroleum ether/ethyl acetate/acetic acid, 3:1:0.1). Crystallisation from diethyl ether. M. p. 132-135°C

A4. 4-Bromo-2,3-dihydro-7-methoxybenzofuran-2-spiro-1'-cyclopentane

To a solution of 8.4 g of A5 in 100 ml of absolute toluene is added 9 g Amberlist 15; the mixture is stirred at 100°C for 10 h. After cooling, the H⁺-ion exchange resin is filtered off and washed with 100 ml methanol. The combined organic solvents are distilled off and the residue is chromatographed on a silica gel column to give 7.4 g of the title compound as a yellow oil. TLC (petrolether/ethyl acetate, 6:4), R_f=0.72.

A5. 2-Cyclopent-1-enylmethyl-3-hydroxy-4-methoxybromobenzene

To a solution of 26.5 g (0.074 mol) methyltriphenylphosphonium bromide in 200 ml of absolute tetrahydrofuran is added dropwise at -89°C under a nitrogen atmosphere 52.1 ml (0.082 mol) of n-butyllithium. Afterwards the suspension is warmed to -30°C, which leads to the dissolution of the suspension. After cooling once again to -70°C, a solution of 19.2 g (0.067 mol) of A6 in 200 ml of absolute tetrahydrofuran is slowly added under a nitrogen atmosphere. Then the mixture is warmed to -10°C and stirred at this temperature for 5 days. TLC (petroleum ether/ethyl acetate, 6:4), R_f (methylene compound)=0.81.

A6. 4-Methoxy-3-(2-oxocycloentyloxy)bromobenzene

To a solution of 20 g (0.1 mol) of 3-Hydroxy-4-methoxybromobenzene in 300 ml of absolute dimethylformamide is added 17.7 g (0.15 mol) of 2-Chlorocyclopentanone and 41.4 g (0.3 mol) of potassium carbonate. The solution is stirred at room temperature for 12 h. Afterwards the solid substances are filtered off and the filtrate is concentrated. The residue is dissolved in 500 ml of ethyl acetate and washed three times with 200 ml of distilled water. The organic layer is dried over sodium sulfate and concentrated. The residue is chromatographed on a silica gel column to give 21.1 g of the title compound as a brown oil. TLC (petrolether/ethyl acetate, 6:4), R_f =0.47.

A7. 6-(4-Hydroxyphenyl)-4,5-dihydro-5-methyl-2H-pyridazin-3-one

Prepared as described by Y. Morisawa et al. (Sankyo Co) EP178189.

A8. (cis)-2-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-carbonyl)-1,2,3,6-tetrahydro-benzolic acid

Prepared from compound A9 and cis-1,2,3,6-tetrahydronaphthalic anhydride as described for compound A3. M. p. 154-156°C

A9. 4-Bromo-2,3-dihydro-2,2-dimethyl-7-methoxybenzofuran

Prepared analogously to compound A4 starting from 3-Hydroxy-4-methoxybromobenzene and 1-chloro- or 1-bromoacetone.

A10. 6-(4-Hydrazinophenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Prepared from compound A11 as described by A. Mertens et al., J. Med. Chem. 1990, 33, 2870-2875.

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A11. 6-(4-Aminophenyl)-5-methyl-4,5-dihydro-2H-pyridazin-3-one

Prepared as described by B.E. Burpitt, L.P. Crawford, B.J. Davies, J. Mistry, M.B. Mitchell and K.D. Pancholi in *J. Heterocyclic Chemistry*, 25, 1689-1695 (1988).

Commercial utility

The compounds according to the invention have valuable pharmacological properties which make them commercially utilizable. As selective inhibitors of type 3 and 4 of cyclic nucleotide phosphodiesterase (PDE3, PDE4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating and cilium-stimulating action but also on account of their respiratory rate- and respiratory drive-increasing action), but on the other hand especially for the treatment of disorders of inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes and of the joints, which are mediated by mediators such as interferons, members of the tumor necrosis factor family, interleukins, chemokines, colony-stimulating factors, growth factors, lipid mediators (e.g., *inter alia*, PAF, platelet-activating factor), bacterial factors (e.g. LPS), immunoglobulins, oxygen free radicals and related free radicals (e.g. nitrogen monoxide NO), biogenic amines (e.g. histamine, serotonin), kinins (e.g. bradykinin), neurogenic mediators (such as substance P, neuropeptide K), proteins such as, for example, granular contents of leukocytes (*inter alia* cationic proteins of eosinophils) and adherent proteins (e.g. integrins). The compounds according to the invention have smooth muscle-relaxant action, e.g. in the region of the bronchial system, of the blood circulation, and of the efferent urinary passages. Furthermore they have a cilium-frequency increasing action, e.g. in the bronchial system.

In this context, the compounds according to the invention are distinguished by low toxicity, good human acceptance, good enteral absorption and high bioavailability, great therapeutic breadth, the absence of significant side effects and good water solubility.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed as therapeutics in human and veterinary medicine, where they can be used, for example, for the treatment and prophylaxis of the following diseases: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of various origin (bronchitis, allergic bronchitis, bronchial asthma, COPD); disorders with a reduction of the cilium activity or with increased demands on the ciliar clearance (bronchitis, mucoviscidose); dermatoses (especially of proliferative, inflammatory and allergic type) such as, for example, psoriasis (*vulgaris*), toxic and allergic contact eczema, atopic eczema, seborrheic eczema, lichen simplex, sunburn, pruritis in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on excessive release of TNF and leukotrienes, i.e., for example, disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), systemic lupus erythematosus, disorders of the immune system (AIDS), including AIDS-related encephalopathies, autoimmune disorders such as diabetes mellitus (Type I, autoimmune diabetes), multiple sclerosis and of the type virus-, bacteria- or parasite-induced demyelinization

diseases, cerebral malaria or Lyme's disease, shock symptoms [septic shock, endotoxin shock, Gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)] and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, faulty immunological reactions in the region of the upper airways (pharynx, nose) and of the adjacent regions (paranasal sinuses, eyes), such as, for example, allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; and also disorders of the central nervous system such as memory disorders and Alzheimer's disease, candidiasis, leishmaniases and leprosy.

On account of their vasorelaxant activity, the compounds according to the invention can also be used for the treatment of high blood pressure disorders of various origin such as, for example, pulmonary high blood pressure and the concomitant symptoms associated therewith, for the treatment of erectile dysfunction or colics of the kidneys and the ureters in connection with kidney stones.

On account of their cAMP-increasing action, however, they can also be used for disorders of the heart which can be treated by PDE inhibitors, such as, for example, cardiac insufficiency, and also as anti-thrombotic, platelet aggregation-inhibiting substances.

The invention further relates to a method for the treatment of mammals including humans who are suffering from one of the above-mentioned diseases. The method comprises administering a therapeutically effective and pharmacologically tolerable amount of one or more of the compounds according to the invention to the sick mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of diseases, especially the diseases mentioned.

The invention also relates to the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the diseases mentioned.

The invention furthermore relates to medicaments for the treatment and/or prophylaxis of the diseases mentioned and which contain one or more of the compounds according to the invention.

It is known to the person skilled in the art that in case of chiral compounds the different diastereomers and enantiomers (in case of two or more chiral atoms) or enantiomers (in case of only one chiral atom) can show different properties.

The term "compounds according to the invention" includes all conceivable pure diastereomers and pure enantiomers, as well as all mixtures thereof independent from the ratio, including the racemates. Preferred are those compounds, in which the hydrogen atoms in the positions 4a and 8a are cis-configurated. Especially preferred in this connection are those compounds, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a.

Advantageously, the substances according to the invention are also suitable for combination with other substances which bring about stimulation of cAMP, such as prostaglandins (PGE2, PGI2 and prostacyclin) and their derivatives, direct adenylylate cyclase stimulators such as forskolin and related substances, or substances indirectly stimulating adenylylate cyclase, such as catecholamines and adrenergic receptor agonists, in particular beta mimetics. In combination, on account of their cAMP degradation-inhibiting action, they in this case display a synergistic, superadditive activity. This comes to bear, for example, in their use in combination with PGE2 for the treatment of pulmonary hypertension.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for antagonizing the effects of the cyclic nucleotide phosphodiesterases of type 3 and 4 (PDE3/4), ameliorating the symptoms of an PDE3/4-mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating PDE3/4-mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula I according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The medicaments are prepared by methods known per se familiar to the person skilled in the art. As medicaments, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries, e.g. in the form of tablets, coated tablets, capsules, suppositories, patches, emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95%.

The person skilled in the art is familiar on the basis of his expert knowledge with the auxiliaries which are suitable for the desired pharmaceutical formulations. Beside solvents, gel-forming agents, ointments bases and other active compound excipients, it is possible to use, for example, antioxidants, dispersants, emulsifiers, preservatives, solubilizers or permeation promoters.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation. For this purpose, these are administered either directly as a

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powder (preferably in micronized form) or by atomization of solutions or suspensions which contain them. With respect to the preparations and administration forms, reference is made, for example, to the details in European Patent 163 965.

For the treatment of dermatoses, the compounds according to the invention are used in particular in the form of those medicaments which are suitable for topical application. For the production of the medicaments, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and additionally processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations which may be mentioned are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The medicaments according to the invention are prepared by methods known per se. The dosage of the active compounds takes place in the order of magnitude customary for PDE inhibitors. Thus topical application forms (such as, for example, ointments) for the treatment of dermatoses contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarily between 0.1 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.01 and 10 mg/kg per day.

Biological investigations

In the investigation of PDE4 inhibition at the cellular level, the activation of inflammatory cells has particular importance. An example which may be mentioned is the FMLP (N-formylmethionylleucyl-phenylalanine)-induced superoxide production of neutrophilic granulocytes, which can be measured as luminol-potentiated chemiluminescence [McPhail LC, Strum SL, Leone PA and Sozzani S, The neutrophil respiratory burst mechanism. In "Immunology Series" 1992, 57, 47-76; ed. Coffey RG (Marcel Decker, Inc., New York-Basel-Hong Kong)].

Substances which inhibit chemiluminescence, and/or cytokine secretion, and/or the secretion of inflammation-increasing mediators in inflammatory cells, like T-lymphocytes, monocytes, macrophages and granulocytes are those which inhibit PDE4 or PDE3 and PDE4. The latter isoenzyme of the phosphodiesterase families is particularly represented in granulocytes. Its inhibition leads to an increase in the intracellular cyclic AMP concentration and thus to the inhibition of cellular activation. PDE4 inhibition by the substances according to the invention is thus a central indicator of the suppression of inflammatory processes. (Giembycz MA, Could isoenzyme-selective phosphodiesterase inhibitors render bronchodilatory therapy redundant in the treatment of bronchial asthma? Biochem Pharmacol 1992, 43, 2041-2051; Torphy TJ et al., Phosphodiesterase inhibitors: new opportunities for treatment of asthma. Thorax 1991, 46, 512-523; Schudt C et al., Zardaverine: a cyclic AMP PDE3/4 inhibitor. In "New Drugs for Asthma Therapy", 379-402, Birkhäuser Verlag Basel 1991; Schudt C et al., Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Ca. Naunyn-Schmiedebergs Arch Pharmacol 1991, 344, 682-690; Tenor H and Schudt C, Analysis of PDE isoenzyme profiles in cells and tissues by pharmacological methods. In "Phosphodiesterase Inhibitors", 21-40, "The Handbook of Immunopharmacology", Academic Press, 1996; Hatzelmann A et al., Enzymatic and functional aspects of dual-selective PDE3/4-inhibitors. In "Phosphodiesterase Inhibitors", 147-160, "The Handbook of Immunopharmacology", Academic Press, 1996.

A. Methodology**1. Inhibition of PDE isoenzymes**

The PDE activity was determined according to Thompson et al. (1) with some modifications (2). The test samples contained 40 mM tris HCl (pH 7.4), 5 mM MgCl₂, 0.5 µM cAMP or cGMP, [³H] cAMP or [³H]cGMP (about 50,000 cpm/sample), the PDE isoenzyme-specific additions described in greater detail below, the indicated concentrations of inhibitor and an aliquot of the enzyme solution in a total sample volume of 200 µl. Stock solutions of the compounds to be investigated in DMSO were prepared in concentrations such that the DMSO content in the test samples did not exceed 1% by volume - to avoid an effect on the PDE activity. After preincubation at 37°C for 5 minutes, the reaction was started by addition of the substrate (cAMP or cGMP). The samples were incubated at 37°C for a further 15 min. The reaction was terminated by addition of 50 µl of 0.2N HCl. After cooling on ice for 10 minutes and addition of 25 µg of 5'-nucleotidase (snake venom from *Crotalus atrox*), the mixture was again incubated at 37°C for 10 min and the samples were then applied to QAE Sephadex A-25 columns. The columns were eluted with 2 ml of 30 mM ammonium formate (pH 6.0). The radioactivity of the eluate was measured and corrected by the corresponding blank values. The proportion of hydrolyzed nucleotide in no case exceeded 20% of the original substrate concentration.

PDE1 (Ca²⁺/calmodulin-dependent) from bovine brain: the inhibition of this isoenzyme was investigated in the presence of Ca²⁺ (1 mM) and calmodulin (100 nM) using cGMP as a substrate (3).

PDE2 (cGMP-stimulated) from rat hearts was purified chromatographically [Schudt et al. (4)] and investigated in the presence of cGMP (5 µM) using cAMP as a substrate.

PDE3 (cGMP-inhibited) and PDE5 (cGMP-specific) were investigated in homogenates of human blood platelets [Schudt et al. (4)] using cAMP or cGMP as a substrate.

PDE4 (cAMP-specific) was investigated in the cytosol of human polymorphonuclear leukocytes (PMNL) [isolated from leukocyte concentrates, see Schudt et al. (5)] using cAMP as a substrate. The PDE3 inhibitor motapizone (1 µM) was used in order to suppress the PDE3 activity emanating from contaminating blood platelets.

2. Statistics

The IC₅₀ values were determined from the concentration-inhibition curves by nonlinear regression using the GraphPad InPlot™ program (GraphPad Software Inc., Philadelphia, USA).

3. References

- (1) Thompson W.J., Terasaki W.L., Epstein P.M. and Strada S.J., Assay of cyclic nucleotide phosphodiesterase and resolution of multiple molecular forms of the enzyme; *Adv. Cycl. Nucl. Res.* **1979**, 10, 69-92
- (2) Bauer A.C. and Schwabe U., An improved assay of cyclic 3',5'-nucleotide phosphodiesterase with QAE Sephadex A-25; *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, 311, 193-198
- (3) Gietzen K., Sadorf I. and Bader H., A model for the regulation of the calmodulin-dependent enzymes erythrocyte Ca^{2+} -transport ATPase and brain phosphodiesterase by activators and inhibitors; *Biochem. J.* **1982**, 207, 541-548.
- (4) Schudt C., Winder S., Müller B. and Ukena D., Zardaverine as a selective inhibitor of phosphodiesterase isoenzymes; *Biochem. Pharmacol.* **1991**, 42, 153-162
- (5) Schudt C., Winder S., Forderkunz S., Hatzelmann A. and Ullrich V., Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Ca; *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1991**, 344, 682-690

B. Results

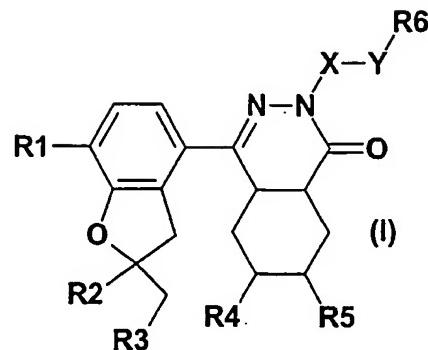
In Table 2 below, the inhibitory concentrations determined according to Section A1 [inhibitory concentrations as -log IC₅₀ (mol/l)] for the compounds according to the invention are indicated for the PDE3 and PDE4 isoenzymes. The numbers of the compounds correspond to the numbers of the examples.

Table2

Compound	PDE4	PDE3
[-log IC ₅₀ mol/l]		
1	8.91	6.90
2	10.35	7.46

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Patent claims

1. Compounds of formula I



in which

R1 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is 1-4C-alkyl and

R3 is hydrogen or 1-4C-alkyl,

or wherein

R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R4 and R5 are both hydrogen or together form an additional bond,

and in which either

X is a covalent bond and

Y is a covalent bond,

or

X is $-C_nH_{2n}-$ and

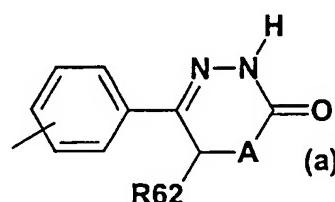
Y is O (oxygen), S (sulfur), carboxylate ($-C(O)-O-$), carboxamido ($-C(O)NH-$) or sulfonamido ($-S(O)_2NH-$),

or

X is phenylene and

Y is carboxylate ($-C(O)-O-$), carboxamido ($-C(O)NH-$) or sulfonamido ($-S(O)_2NH-$),

R6 represents a radical of formula (a)



wherein

- A is S (sulphur) or -CH(R61)-,
 - R61 is hydrogen or 1-4C-alkyl,
 - R62 is hydrogen or 1-4C-alkyl, or wherein
R61 and R62 together form an additional bond,
 - n is an integer from 1 to 6,
- and the salts of these compounds.

2. Compounds of formula I according to claim 1 in which

R1 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R2 is 1-4C-alkyl and

R3 is hydrogen or 1-4C-alkyl,

or wherein

R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

R4 and R5 are both hydrogen or together form an additional bond,

and in which either

X is a covalent bond and

Y is a covalent bond

or

X is -C_nH_{2n}- and

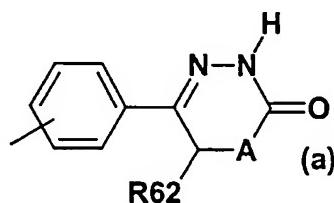
Y is O (oxygen), carboxamido (-C(O)NH-) or sulfonamido (-S(O)₂NH-),

or

X is phenylene and

Y is carboxamido (-C(O)NH-) or sulfonamido (-S(O)₂NH-),

R6 represents a radical of the formula (a)



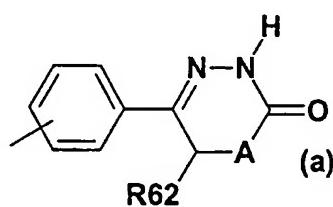
wherein

- A is S (sulphur) or -CH(R61)-,
- R61 is hydrogen or 1-2C-alkyl,
- R62 is hydrogen or 1-2C-alkyl, or wherein

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R61 and R62 together form an additional bond,
 n is an integer from 1 to 6,
 and the salts of these compounds.

3. Compounds of formula I according to claim 1 in which
 R1 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,
 R2 is 1-4C-alkyl and
 R3 is hydrogen or 1-4C-alkyl,
 or wherein
 R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane or cyclohexane ring,
 R4 and R5 are both hydrogen or together form an additional bond,
 and in which either
 X is a covalent bond and
 Y is a covalent bond
 or
 X is $-C_nH_{2n}-$ and
 Y is O (oxygen) or carboxamido ($-C(O)NH-$)
 or
 X is phenylene and
 Y is carboxamido ($-C(O)NH-$),
 R6 represents a radical of formula (a)



wherein

- A is S (sulphur) or $-CH(R61)-$,
 R61 is hydrogen,
 R62 is methyl, or wherein
 R61 and R62 together form an additional bond,
 n is an integer from 1 to 6,
 and the salts of these compounds.

4. Compounds of formula I according to claim 1 in which

- R1 is methoxy or difluoromethoxy,
 R2 is methyl,

R3 is hydrogen,

or wherein

R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane ring,

R4 and R5 together form an additional bond,

and in which either

X is a covalent bond and

Y is a covalent bond

or

X is $-C_nH_{2n}-$ and

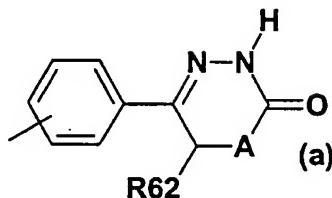
Y is O (oxygen) or carboxamido ($-C(O)NH-$)

or

X is phenylene and

Y is carboxamido ($-C(O)NH-$),

R6 represents a radical of formula (a)



wherein

A is S (sulphur) or $-CH(R61)-$,

R61 is hydrogen,

R62 is methyl, or wherein

R61 and R62 together form an additional bond,

n is an integer from 1 to 6,

and the salts of these compounds.

5. Compounds of formula I according to claim 1 in which

R1 is methoxy,

R2 is methyl,

R3 is hydrogen,

or wherein

R2 and R3 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane ring,

R4 and R5 together form an additional bond,

and in which either

X is a covalent bond and

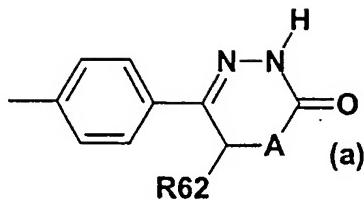
Y is a covalent bond

or

X is -(CH₂)₆- and

Y is O (oxygen),

R6 represents a radical of formula (a)



wherein

A -CH(R61)-,

R61 is hydrogen,

R62 is methyl,

and the salts of these compounds.

6. Compounds of formula I according to one of the claims 1 to 5 which have according to the rules of Cahn, Ingold and Prelog the absolute configuration S in the position 4a and R in the position 8a.

7. Medicaments containing one or more compounds of formula I according to claim 1 together with the usual pharmaceutical auxiliaries and/or carrier materials.

8. Medicaments containing a compound of formula I according to claim 6 together with the usual pharmaceutical auxiliaries and/or carrier materials.

9. Compounds of formula I according to claim 1 for use in the treatment of illnesses.

10. Use of compounds of formula I according to claim 1 for the production of medicaments for the treatment of airway disorders.

INTERNATIONAL SEARCH REPORT

Intern'l Application No

PCT/EP 00/08900

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D405/14 C07D417/14 A61K31/50 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 31090 A (BYK GULDEN LOMBERG CHEM FAB ; ULRICH WOLF RUEDIGER (DE); STERK GEERT) 24 June 1999 (1999-06-24) cited in the application claim 1 ---	1-7
Y	WO 98 31674 A (BYK GULDEN LOMBERG CHEM FAB ; STERK GEERT JAN (NL)) 23 July 1998 (1998-07-23) cited in the application claim 1 ---	1-7 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

13 November 2000

Date of mailing of the international search report

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Steendijk, M

INTERNATIONAL SEARCH REPORT

Intern'l Application No

PCT/EP 00/08900

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>COATES ET AL: "1,4-Bis(3-oxo-2,3-dihydropyridazin-6-yl)b enzene analogs: potent phosphodiesterase inhibitors and inodilators" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 33, no. 6, 1990, pages 1735-1741, XP002119282 ISSN: 0022-2623 the whole document ---</p>	1-7
A	<p>DATABASE WPI Section Ch, Week 198830 Derwent Publications Ltd., London, GB; Class B03, AN 1988-209101 XP002131854 & JP 63 145272 A (MORISHITA PHARM CO LTD), 17 June 1988 (1988-06-17) abstract ---</p>	1-7
P,Y	<p>WO 99 47505 A (BYK GULDEN LOMBERG CHEM FAB ;STERK GEERT JAN (NL); MEY MARGARETHA) 23 September 1999 (1999-09-23) claim 1 -----</p>	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

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JP 63145272	A	17-06-1988		NONE		
WO 9947505	A	23-09-1999	AU	3328499 A		11-10-1999